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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/505,137	04/25/2005	Parveen Bhatarah	1581.1120000/RWE/FRC	1688

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EXAMINER	
KAROL, JODY LYNN	

ART UNIT	PAPER NUMBER
1627	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,137	BHATARAH ET AL.	
	Examiner	Art Unit	
	Jody L. Karol	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/25/2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *77-80 and 82-98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *77-80 and 82-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of applicant's Amendment/Remarks filed 3/25/2010. Claims 77 and 94 have been amended. Claims 1-76, 81, and 96-106 are cancelled. Claims 77-80 and 82-98 are pending and are currently under consideration.

WITHDRAWN REJECTIONS

1. In view of Applicant's amendment to claims 77 and 94, the rejection of claims 77-80 and 82-98 under 35 U.S.C. 112, 2nd paragraph, as being indefinite is herein withdrawn.

MAINTAINED REJECTIONS

2. The following rejections have been maintained from the previous Office Action dated 10/26/2009, but have been slightly modified to account for Applicant's amendments:

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 77-80, and 82-98 rejected under 35 U.S.C. 103(a) as being unpatentable over Harris et al. (US 6,187,765 B1).

The instant claims are directed to methods for preparing sterile pharmaceutical compositions of the steroid, budesonide, comprising dissolving the non-sterile steroid in a solvent to yield a solution of the steroid; filtering the solution to yield a sterile solution; combining the sterile solution with sterile water to form a suspension; optionally removing all or part of the solvent; treating the suspension to obtain a particle size

distribution having a mass median diameter less than 10 μm; under sterile conditions combining said suspension with a pharmaceutically acceptable carrier to yield a sterile composition; and storing said composition in a sterile container.

Harris et al. teaches aqueous suspensions of water-insoluble pharmaceutical substance intended for inhalation therapy (see column 1, lines 12-15). Harris further teaches in Example 1, a method of preparing a sterile suspension of a steroid, mometasone furoate, comprising dissolving said steroid in acetone, a class 3 solvent as claimed in the instant claim 83; filtering said solution through a sterilizing filter, such as a filtration medium having pore sizes not exceeding 0.2 μm in diameter, as claimed in the instant claims 89 and 96, into a sterile vessel; heating said sterile solution to about 45-50 °C and slowly adding sterile purified water over 15 min.; while maintaining the temperature and more of the sterile water and stir for 30 min.; continuing to maintain the temperature and stir for another 30 min. during which a precipitate forms; slowly adding more water and stirring for 60 min. at the elevated temperature; stirring at 60 min. at the elevated temperature; cooling the mixture to ambient temperature while stirring; filtering said precipitate and washing with water; and drying under vacuum to yield dry sterile mometasone furoate (see column 6, lines 25-62). The sterile mometasone furoate is then added to a sterile carrier solution comprising polysorbate (a surfactant) as claimed in the instant claim 90, to form a suspension; said suspension is passed through a Microfluidizer to yield a suspension with a median particle size of 1.24 as claimed in the instant claims 91 and 97 (see column 7, lines 65-68); and the sterile suspension is

transferred to sterile containers for use in a nebulizer (i.e. an ampoule as claimed in the instant claim 93) (see column 6, line 64 to column 7, line 36).

Harris et al. do not teach a method wherein part or all of the non-aqueous solvent is removed from the aqueous suspension. However, this step is considered to be optional. Moreover, the steps of removing the solvent by filtration, drying the steroid, and then reconstituting with purified, sterilized water and carrier components to form an aqueous suspension are not excluded by the claim language because the term "comprising" is interpreted as broad and open. Furthermore, the isolation of the product is not deemed as essential because it does not materially affect the end product.

Harris et al. does not teach a method of preparing a sterile suspension of steroid where the steps are in the same order as claimed. Specifically, Harris et al. teaches the sterile suspension is combined with a carrier before the suspension is treated to obtain the desired particle size, whereas the carrier is added after the sterile suspension is treated to obtain the desired particle size in the instant claims. However, it has been held that merely reversing the order of steps in a multi-step process is not a patentable modification absent unexpected or unobvious results. *Ex Parte Rubin*, 128 USPQ 440 (Bd. App. 1959). See also *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946). Thus, adding the carrier after the suspension is treated to obtain the desired particle size instead of before is deemed as an obvious modification absence evidence to the contrary.

Harris et al. also does not teach a method for preparing a sterile suspension of steroid wherein the steroid is budesonide. However, Harris et al. does teach that

aqueous suspensions of drug particles for nebulization are known, and mentions budesonide as a commercially available product (see column 2, lines 5-12). Harris et al. also teaches that formulations that are to be inhaled must be free of pathogenic organisms, and thus be prepared and handled under sterile conditions (see column 3, lines 7-10).

It would have been obvious to one of ordinary skill in the art to substitute budesonide for mometasone furoate as the steroid in the method taught by Harris et al., to produce a sterile suspension of budesonide. One of ordinary skill in the art would have been motivated to do so in order to produce an inhalable formulation of budesonide free of any potential pathogenic organisms. One of ordinary skill in the art would have had a reasonable expectation of success in producing a sterile suspension of budesonide because Harris et al. teach a method of producing aqueous suspensions for inhalation of the corticosteroid mometasone furoate.

In regards to the instant claims 78-79, wherein the budesonide steroid is a powder or micronized power, Harris et al. does not explicitly teach using a powder steroid, or a micronized powder sterile to prepare the sterile suspensions. However, it would have been obvious to one of ordinary skill in the art at the time of invention to use a powder or micronized powder of the steroid to prepare the sterile suspensions because powders and micronized powders have an increased surface area. One of ordinary skill in the art would have been motivated to increase the surface area of the steroid to increase the rate at which the steroid dissolves in the solvent.

In regards to claims 82, 84, and 95, Harris et al. does not teach dissolving the steroid in alcohol or a class 2 solvent. Harris et al. teaches dissolving the steroid in acetone (as described *supra*). However, it is been held that the selection of a known material based on its suitability for its intended use supported a *prima facie* case of obviousness determination in *Sinclair & Carroll Co. V. Interchemical Corp.*, 325, US 327, 65 USPQ 297 (1945). Accordingly, since alcohol and class 2 solvents are known solvents, it would have been obvious to one or ordinary skill in the art at the time of the invention to select an appropriate solvent to dissolve the steroid.

In regards to the instant claim 85-86, the boiling point of acetone is 56.5°C. Harris et al. teaches dissolving the steroid at 45-50°C which is significantly overlaps with the range as claimed in the instant claim 85. Harris et al. does not teach adding the steroid to the solvent wherein the solvent is at reflux. However, it would have been obvious to one of ordinary skill in the art at the time of the invention to add the steroid to the solvent at reflux. One of ordinary skill in the art would have been motivated to do so to increase the rate at which the steroid dissolves in said solvent.

In regards to claims 87, Harris et al. does not teach removing the solvent under reduced pressure. Acetone (the solvent taught by Harris et al.) will evaporate on its own at room temperature to a certain extent. Heating any solvent or reducing the pressure any solvent is kept at, will increases the rate at which the solvent evaporates. Harris et al. heats the acetone (see column 6, lines 37-40). Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to remove the

solvent under reduce pressure. One of ordinary skill in the art would have been motivated to do so to increase the rate of solvent removal.

In regards to the instant claims 92 and 98, Harris et al. does not explicitly teach steroid particles in the suspension having a mass median diameter in the range of 2-3 μm. However, Harris et al. does teach that the preferred average particle size for inhaled particles is 0.5 to 5 μm (see column 1, lines 27-43 and column 2, lines 65-67). Furthermore, Harris et al. claims suspensions where the particle size is less than 5 μm, which significantly overlaps with range as claimed (see column 10, claim 14), and teaches suspensions where the median particle size is 1.24 μm. In this case, where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 UPSQ 90 (CCPA 1976). Furthermore, while the references do not explicitly teach the claimed particle size range, it is the Examiner's opinion that the determination of optimal or workable particle size range by routine experimentation is obvious absent showing of criticality of the claimed particle size range. One having ordinary skill in the art would have been motivated to do this to obtain an optimal particle size for inhaled steroids.

Therefore, the invention as a whole would have been *prima facie* obvious to one skilled in the art at the time it was made.

Response to Arguments

5. Applicant's arguments filed 3/25/2010 have been fully considered but they are not persuasive.

Applicant argues the method does not and cannot comprise an intermediate drying step because the step would be in conflict with a method which yields an aqueous suspension of pharmaceutical composition as required by claims 77 and 94. Specifically, Applicant argues that amended claims 77 and 94 do not include any drying step, that each step of the method utilizes the solution or suspension obtained in a preceding step, and that the step of removing the non-aqueous solvent (step iv) occurs only after water has been added to form an aqueous suspension with the steroid. In response it is respectfully submitted that the while the instant claims do not include any drying steps, they are not excluded by the claim language because the term "comprising" is interpreted as broad and open. Furthermore, isolating the product and reconstituting with purified, sterilized water and pharmaceutical carrier components as taught by Harris et al. results in a substantially equivalent aqueous suspension as formed by step (iv). It is also noted that Harris et al. do teach adding water prior to form a suspension prior to solvent removal and isolation (see column 6, lines 38-62), and thus the removal of the non-aqueous solvent does occur after water has been added to form a suspension as instantly claimed in step (iii).

The Applicant notes that on page 7 of the Office Action, the Examiner stated that Example 1 of Harris teaches a method of preparing a sterile suspension of steroid. The Applicant argues that Example 1 of Harris produces sterile mometasone furoate by process that finishes with a dry step to produce a dry product, and that Example 1 does not result in the production of a sterile suspension. In response it is respectfully submitted that while page 7 states Example 1 of Harris teaches a method of preparing

the a sterile suspension, steps described in the Office Action of pages 7-8 are the steps of Examples 1 and 2 as taught by Harris, wherein Example 2 results in sterile suspension of steroid. The rejection has been corrected to reflect the correct Examples taught by Harris et al. as originally described in the 12/11/2009 Office action.

The Applicant argues that it would not be obvious for the skilled artisan to the combine the processes of Example 1 and 2 of Harris by omitting the drying step of Example 1 because if the mometasone furoate monohydrate were to remain in suspension, there would be a number of problems including: (i) the presence of acetone in suspension and (ii) the mometasone would be in dilute suspension comprising a large amount of water making it difficult to calculate the precise amount of mometasone present. The Applicant contends that dilute suspension could not simply be added to the excipients prepared in steps 1 and 2 of Example 2 without a significant number of calculations and alterations to the process of Example 2. In response it is respectfully submitted that the solvent removal (step (iii) in the instant claims) is optional, and thus the presence of acetone is not precluded by the claim language. Further, in response to Applicant's argument that it would be difficult to calculate the precise amount of mometasone furoate monohydrate in the suspension, it is noted that the amount s are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Alternatively, merely scaling up Example 2 to accommodate the amount of steroid utilized in Example 1 is deemed to be within the purview of the ordinary artisan.

The Applicant further argues that if Example 2 is directly followed as taught in Harris, the dry pharmaceutical component is only dissolved in aqueous solution. There is no use of non-aqueous solvent in Example 2, and therefore no step in which non-aqueous solvent is removed from aqueous suspension comprising the pharmaceutical component and water as required by claims 77 and 94 of the instant application. The Examiner respectfully disagrees. The removal of the non-aqueous solvent in step (iv) is an optional step, and thus not required by the instant claims. Furthermore, the addition of the non-aqueous solvent is taught in Example 1 of Harris et al.

The Applicant argues that a skilled artisan reading Harris et al. would understand that the two stage method is essential and moreover, even if they were seeking a simpler method, it would not be obvious to make significant amendments to both parts of the Harris method in order to combine the separate processes. The Applicant further states that Harris et al.'s teaching that "[i]t is preferred to produce the mometasone furoate monohydrate under sterile conditions, conduct the drug micronization in a sterile environment, and perform a sterile packing operation" provides additional direction to the skilled artisan that the processes of Harris are separate and distinct parts of an at least two stage method. In response it is respectfully submitted that the isolation of the steroid is a design choice and not an essential step because it does not materially affect the end product. Solid products are often isolated because they are easier to transport that the suspended products. However, when the solid product is to be immediately processed into the final suspended product for use in a nebulizer, it would be obvious to the ordinary artisan to leave the steroid product in the water-based suspension for the

further processing steps, and scale the method steps up/down to the amount of steroid utilized. Alternatively, as stated *supra*, the "comprising" language of the instant claims does not exclude the isolation and drying steps taught by Harris et al. Further, it is also noted that the instant claims are considered to produce a steroid under sterile conditions, conduct the drug micronization in a sterile environment, and perform a sterile packing operation. Thus, it is not convincing that the statement by Harris et al. provides direction to the skilled artisan that the processes must necessarily be separate and distinct parts of at least a two-stage method.

Thus, for these reasons, Applicant's arguments are found unpersuasive. Said rejection is maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jody L. Karol whose telephone number is (571)270-3283. The examiner can normally be reached on 8:30 am - 5:00 pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Jody L. Karol/

Examiner, Art Unit 1627

/Yong S. Chong/
Primary Examiner, Art Unit 1627